Lipid membranes : Theory and simulations bridged to experiments

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2016

Vattulainen , I T & Rog , T J 2016 , ' Lipid membranes : Theory and simulations bridged to experiments ' , Biochimica et Biophysica Acta. Biomembranes , vol. 1858 , no. 10 , pp. 2251-2253 . https://doi.org/10.1016/j.bbamem.2016.06.007

http://hdl.handle.net/10138/311778
https://doi.org/10.1016/j.bbamem.2016.06.007

Vattulainen and Tomasz Róg Biochimica et Biophysica Acta 1858 (2016) 2251–2253
http://dx.doi.org/10.1016/j.bbamem.2016.06.007

Preface to Special Issue entitled: "Lipid membranes: Theory and simulations bridged to experiments"

There are essentially five classes of molecules that are the corner stones of life. DNA in terms of nucleic acids contains the information of building proteins that are the nanoscale engines working in water as well as in membranes, the latter being largely comprised of lipids and carbohydrates. The importance of all of these molecular classes in generating cellular functions has been recognized a long time ago, yet lipids remained aside from the limelight for a number of years. The paradigm changed largely in the 1990s, when the idea of lipids being involved in the activation of membrane proteins was given more and more attention. Meanwhile, the concept of lipidomics was introduced in 2000, and the first discoveries of membrane protein structures that contained lipids as integral components of the protein structure were made about 20 years ago. Given these, it seems that the considerable appreciation of the importance of lipids in dictating and modulating a variety of cellular functions such as those emerging from membrane proteins started roughly ~20 years ago.

Most of the lipids are in membranes, and there are many different lipid types. Given that nature does not do anything without a good reason, all the thousands of different lipids apparently, have a function. At the moment we understand only a tiny fraction of those, however due to the improving experimental and theoretical methodology the situation is getting better rapidly. Here, a close interplay between experiments and theoretical work is called for. Interpretation of experimental data is often complicated or even impossible without a solid theoretical framework, and the resolution of experimental bioimaging techniques is still too limited to see what exactly happens in nanoscale membrane processes and why. This is where computer simulations can provide a great deal of added value. The quality of atomistic simulation models is improving all the time, and the development of new simulation techniques together with increasing computational capacity allows one to explore membrane structures and processes over larger and larger scales through models whose complexity approaches the reality explored experimentally in native conditions.

Researchers are intriguing folks; they are in the habit of making the impossible possible. Given this, it is exciting to see the progress in our field in the near future, namely how the simulation models of complex native-like membranes approach the systems studied by cell biologists under in vivo conditions. What is clear at the moment is that there is a continuous need for a joint interplay and

discussion between theory and experiments. We need new ideas and methods to narrow the gap between simulations and experiments. Simulations need experiments to develop better models, and experiments need theory and high-quality simulation models to guide the interpretation of experimental data.

In this Special Issue, we consider recent developments in biomolecular simulations of lipid membrane systems. We discuss the progress made in atomistic simulations as well as in considering lipid systems through more simplified, so-called coarse-grained molecular simulation models. A great deal of attention in this Special Issue is paid to methodological development that guides us to improve simulation models and to broaden their scope. In many of these articles, the authors discuss concretely how simulations can be bridged to experiments. Indeed the best way to prepare and carry out simulations is to couple them to experiments as tightly as possible, therefore we also consider a few experimental tech niques and fields that have a lot of potential to foster progress in developing more accurate and efficient simulation models, which in turn would generate considerable added value to experimental science.

1. Atomistic simulations of lipid membrane systems

One of the main functions of lipid bilayers is to isolate cells from their environment. Therefore, membrane permeability for water, gases, and other small molecules such as xenobiotics is one of the key properties of lipid bilayers. In this context, Shinoda in this Special Issue discusses the insight gained through atomistic molecular dynamics (MD) simulations of intact lipid membranes [1]. Meanwhile, permeation of larger molecules through lipid bilayers typically requires pore formation, which is considered in the article by Kirsch and Böckmann [2]. They discuss how an external electric field, ion imbalance, antimicrobial peptides, and surfactants give rise to pore formation, and how the pores facilitate transmembrane transport. Casciola and Tarek in turn concentrate in particular on pores formed by an electric field, and how the pores are involved in the transfer of siRNA [3]. Another important process dealing with permeation of gases through lipid bilayers is discussed in detail in the article by Mayne et al. [4]. The water-membrane interface is a highly dynamic nanoscale region that contributes significantly to the binding of peripheral membrane proteins and numerous small molecules with membrane surfaces. In the article by Pasenkiewicz-Gierula et al. [5], the key interactions between lipid head groups, water, and ions as well as their networks are discussed in full. Pasenkiewicz-Gierula et al. also provide a concrete example of polymyxin B that is one of

antimicrobial compounds interacting with lipid headgroups. This discussion is extended in the paper by Mayne et al. [4], which presents an overview of the behavior of anesthetics, drugs, and hormones at the interfacial region of membranes. Charged lipids play a role in numerous biological functions and membrane properties, such as in modulating membranes' structural properties and the interactions between membranes and integral and peripheral membrane proteins, nanoparticles, drugs, and neurotransmitters. Pöyry and Vattulainen [6] discuss this broad topic largely from a computational perspective, including also a comparison to experiments when that is only possible. Lipid assemblies such as micelles and liposomes have numerous applications. In this context, Bunker et al. [7] discuss how PEGylated lipids can be used as drug delivery carriers. Meanwhile, Faller [8] presents a survey of lipid probes' applications and their effects on lipid bilayer properties. Examples of synthetic lipids and their pharmacological applications are discussed in the article by Kepczynski and Róg [9], and gold nanoparticles interacting with lipid bilayers and their numerous biomedical applications are discussed in the article by Rossi and Monticelli [10]. Lipid-protein interactions are known to be decisive for the activation of various membrane proteins. A comprehensive review of MD simulation studies of these interactions and their implications is given in the article by Hedger and Sansom [11]. Pan and Segrest, in turn, review studies of lipoproteins composed of a nanoscale lipid droplet surrounded by proteins attached to the lipid droplet surface [12]. Lipoproteins play a major role in our health in the context of cardiovascular diseases, and here, too, it is important to understand how lipids are involved in these conditions.

2. Large-scale modeling through coarse-grained systems

Biological systems are often characterized by time and length scales not accessible by current atomistic simulations. Simulations of coarse-grained models provide a means to lower the computational load and thus to extend the scales to explore systems and phenomena that one cannot yet study by atomistic simulations. Tear film layers and lung surfactants discussed in the articles by Cwiklik [13] and Baoukina and Tieleman [14], in respective order, are examples of complex large-scale structures, where simulations of coarse-grained models provide new and aluable insight. As to dynamical aspects, diffusion of lipids and proteins in complex and crowded membrane environments is discussed in the articles by Guigas and Weiss [15] and Metzler et al. [16]. These papers that deal with (hydrodynamic long-time scale) diffusion as well as anomalous diffusion bring up examples of highly relevant processes characterized by time scales that at the moment are accessible only to coarse-grained model simulations.

3. Development of simulation methodology for studies of membranes

Breakthroughs in science often emerge from development of new methods and technologies. The simulation methods and models are in continuous development, thus the third section of this Special Issue is devoted to articles providing insight into recent progress and open issues in the field. The article by Javanainen and Martinez-Seara [17] gives an overview of existing software packages and tools that are available for preparation, performing, and analysis of biomolecular simulations of lipidbased systems. Of particular importance is the authors' conclusion that the software and the particular implementation of algorithms used in the simulations affect the quality of force field performance, thus the models of lipids are not fully transferable between the many simulation packages. Recent development of lipid force fields is presented in the article by Lyubartsev and Rabinovich [18]. A comparison of two coarse-grained force fields (MARTINI and ELBA) for studies of oxidized lipids is presented in the article by Siani et al. [19]. The challenges of force field validation are partially discussed in ref. [18] and further elucidated in more detail in the review by Ollila and Pabst [20], who concentrate on validation of simulation models against the data given by two experimental techniques: nuclear magnetic resonance and x-ray and neutron scattering, which provide parameters which can be directly calculated from MD simulations. Meanwhile, MD simulations, like any technique, are also prone to errors and artifacts. This important topic is discussed by Wong-ekkabut and Karttunen [21] and also in the paper by Neale and Pomès [22], who consider problems resulting from sampling errors in free energy calculations.

4. Advances in experimental methodology, supporting molecular membrane simulations

Experiments can live without simulations, but theory and simulations would not survive without experiments. Alternatively one can say that the reality of simulation models could be questioned if simulations would have no coupling to experiments. Given this, the coupling between experimental and theoretical studies is clearly of high importance to validate the simulation models [20] and to make sure that simulations yield predictions that can also be tested by experiments. In this context, Dafforn et al. [23] discuss recent progress in the field of membrane protein structure determination, a topic that is crucial for the simulation field since there is no reliable way to theoretically study the role of lipids in membrane protein function unless one knows the protein structures in the first place. The article by Eggeling and Honigmann [24] continue this discussion by focusing on super-

resolution microscopy methods. Bioimaging is one of the outstanding ways to elucidate the dynamics taking place in complex lipid membrane structures, thus there is reason to develop ways to bridge the gap between superresolution microscopies and biomolecular simulations, and to foster their interplay to better understand what really happens in complex membranes and why. Finally, in the same spirit, the article by Simons [25] presents an overview of membrane complexity, which in part emerges from the variety of lipids that contribute to the modulation of membrane protein activation and function. Progress in lipidomics is one of the keys to extend the scope of molecular simulations and to render the simulation models as realistic as possible. Altogether, the present Special Issue comprises a large number of excellent articles that outline the current state of the art in lipid membrane simulations, and also brings forward several emerging experimental techniques and fields that have potential to foster the field of lipid simulations. Hopefully these articles will attract more and more attention to the exciting world of lipids.

We wish to dedicate this Special Issue to Dr. Marja Hyvönen, our friend and colleague, who passed away in January 2016.

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